
KCC2 rescues functional deficits in human neurons derived from patients with Rett syndrome.

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Public Summary:

This article describes the use of induced pluripotent stem cells from patient with Rett syndrome as a prototype to study autism spectrum disorders. Together with our collaborators, we found that Rett-derived neurons have defects during maturation. The molecular mechanism described here can potentially explain the regression phase in Rett and autism.

Scientific Abstract:

Rett syndrome is a severe form of autism spectrum disorder, mainly caused by mutations of a single gene methyl CpG binding protein 2 (MeCP2) on the X chromosome. Patients with Rett syndrome exhibit a period of normal development followed by regression of brain function and the emergence of autistic behaviors. However, the mechanism behind the delayed onset of symptoms is largely unknown. Here we demonstrate that neuron-specific K(+)-Cl(-) cotransporter2 (KCC2) is a critical downstream gene target of MeCP2. We found that human neurons differentiated from induced pluripotent stem cells from patients with Rett syndrome showed a significant deficit in KCC2 expression and consequently a delayed GABA functional switch from excitation to inhibition. Interestingly, overexpression of KCC2 in MeCP2-deficient neurons rescued GABA functional deficits, suggesting an important role of KCC2 in Rett syndrome. We further identified that RE1-silencing transcriptional factor, REST, a neuronal gene repressor, mediates the MeCP2 regulation of KCC2. Because KCC2 is a slow onset molecule with expression level reaching maximum later in development, the functional deficit of KCC2 may offer an explanation for the delayed onset of Rett symptoms. Our studies suggest that restoring KCC2 function in Rett neurons may lead to a potential treatment for Rett syndrome.

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